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Clinical commentary

Talc and ovarian cancer

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HIGHLIGHTS

- Talc use has been linked to the risk of ovarian cancer in many case-control studies.
- Genital talc use is much less common now than it was in earlier cohorts of women in North America.
- It is not possible to say that any specific case of ovarian cancer was the result of talc use.

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Interest in a possible link between talcum powder and ovarian cancer risk dates back to the 1960s when the public was concerned about asbestos contamination in talc. Talc has been in the news intermittently since then, but the story of talc and ovarian cancer made the front page in February 2016, when the family of an ovarian cancer patient successfully sued Johnson and Johnson for 72 million dollars. This surprising jury decision raises a few questions. Is there a real and robust statistical association between talc use and ovarian cancer, and if so, is the association causal or due to confounding? What is the risk of cancer associated with talc use and how do we tell if a particular case of ovarian cancer was caused by talc? What should we tell our patients?

Most of the evidence comes from case-control studies. In 2013, the Ovarian Cancer Association Consortium pooled eight of these and analysed 8525 cases and 9859 controls [1]. They reported that genital powder use was associated with a modest but significant increased risk of epithelial ovarian cancer (OR = 1.24; 95% CI 1.15–1.33). The association between talc and ovarian cancer was significant in five of the eight individual studies. More recently, Cramer et al. studied 2041 cases and 2100 controls (some of whom were included in the OCAC study) [2]. They estimated the risk of ovarian cancer associated with genital talc use to be 1.33 (95% CI 1.16 to 1.52) The case-control studies to date are consistent; given the small effect size it is not surprising that some are positive (i.e., show a significant increase in risk) and some are negative (i.e., show a non-significant increase in risk or no risk difference). Some say, based on this data, that there is little or no evidence that talc is associated with ovarian cancer. This is a conservative opinion, based on an uncompromising interpretation of statistics and a demand for proof. For the sake of argument, let us suppose that the true risk ratio for ever use of talc and the development of ovarian cancer is 1.2. This estimate is the one generated from the large pooling study [1] and is the level of risk that is under discussion the media. It is possible that the true risk might be lower or higher than this single estimate. In this scenario, where talc increases the risk of ovarian cancer by 20% beyond the baseline of 1.3% lifetime, it would be challenging to convince the epidemiology community that there is a danger. Simply put, a risk ratio of this size falls outside the resolution of most epidemiologic studies; for example, if we set the *p*-value for significance at 0.05, then, in order to have a power of 0.80 to discriminate an increase in risk of 20%, and if 20% of the population is exposed to talc, we would require a case-control study of 2801 cases and 2801 controls. This is a very large sample for a case-control study, especially given that ovarian cancer is rare and only but the large study of Cramer et al the pooled analyses of OCAC were designed to detect and odds ratios this small [1,2]. If the

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magnitude of the association is to be estimated with precision it is important that consortia are develop and expanded in order to generate the appropriate sample size.

Prospective observational studies are less prone to bias than case-control studies, and for this reason they are given greater weight. In particular, they are not prone to recall bias (where the accuracy of the recollection of the exposure differs between cases and controls); selection bias (where the unexposed and exposed women are not equally likely to be ascertained for study) and survivorship bias (which would occur if the survival of women with ovarian cancer differs, depending on prior talc exposure. In the Nurses Health Study, 78,630 women were followed for a mean of 12.9 years [3]. There were 307 ovarian cancers diagnosed in the follow-up period. There was no overall association with ever-use of talc (HR = 1.09; 95% CI 0.86 to 1.37, but there was a modest and significant increased risk for serous ovarian cancer (HR = 1.40; 95% CI; 1.02–1.91). These figures could be dismissed as non-significant or as due to chance, but if the real risk were in fact 1.2, this is about what we would expect. In the Women's Health Initiative [4], 61,285 women were followed for an average of 12.4 years. 53% of the women reported perineal talc use (a very high proportion). The adjusted hazard ratio for serous ovarian cancer was 1.13, but this was not significant (95% CI 0.84 to 1.51). Neither prospective study confirmed the association of talc use and ovarian cancer raised by the case-control studies, but neither study was powered to detect a risk of 1.2 and therefore we cannot exclude the possibility. Only two women in a thousand will develop ovarian cancer in a ten-year follow up period. If we study 10,000 women over 10 years we can expect 20 cancers to occur. If the true odds ratio is 1.2, we will expect 20 cancers in an unexposed group of 10,000 women and 24 cancers in an exposed group of equal size and this difference will not be significant ($p = 0.65$). In order to achieve statistical significance in a prospective study, we need a much larger cohort, e.g., we will need to study upwards of 200,000 women for ten years.

Given this inherent limitation of cohort studies, it is not surprising that we have not been able to confirm the case-control studies with prospective studies, but this does not mean that the case-control studies were wrong. I don't think it is because the prospective studies are free from the biases that plague the case-control studies (e.g., recall bas) — I think the parsimonious explanation is that they lack statistical power. It is well that we also consider various possible biases as a source of imprecision in case-control studies. In the case of talc and ovarian cancer we should consider recall bias, survivorship bias and confounding bias. The idea behind recall bias is that a case is more likely to (correctly) recall the past use of talc than a control (who might forget) or that a case is more likely than a control to (incorrectly) report the use of talc that was never used. In studies where simple exposures that are coded as never/ever use recall bias unlikely to be an important source of bias. Survivorship bias would occur if we used prevalent cases and the use of talc was associated with better or worse survival, once ovarian cancer develops. There is no reason to assume that this is the case.

Confounding bias may be more subtle. When people say that 'association is not causality' they mean to say that that talc may not actually cause ovarian cancer but both talc and ovarian cancer may be linked to a third factor such as birth control pills — perhaps women who use talc are less likely to use birth control pills and therefore form a high risk group. Hardly likely — and the other risk factors for ovarian cancer are parity, breast feeding and tubal ligation. None of these are a priori likely to be confounders and in any case, most case-control studies will adjust for these. The most important potential confounder is year of birth (see below) and it is critical to control for this. It is unlikely that the association between talc and ovarian cancer is due to confounding and so it is fair to say that if there is a statistically robust relationship between talc use and ovarian cancer it is likely to be causal (albeit with intermediate factors such as inflammation). In any case, given the number of hazard ratios reported in the literature between 1.1 of 1.4 in both case-control and cohort studies, it is disingenuous to state that there is *no evidence* that talc is associated with ovarian cancer.

It has been suggested that talc passes through the cervix and endometrium and becomes lodged in the fallopian tube where it induces an inflammatory reaction [5]. This is hypothetical, but is supported by the observation of talc particles within the pelvic organs [6] and fits with the paradigm that most serous ovarian cancers originate in the fallopian tube and that intra-epithelial lesions in the fallopian epithelium are the earliest manifestations of an impending ovarian cancer [7]. If the model is correct, it is possible that the passage of talc is aided by retrograde menses and that talc use during menses poses a special risk. This might explain in part why the association between talc applied to sanitary napkins and ovarian cancer is among the most consistent. Against the model is the observation that, in the prospective studies, the relative risk of cancer associated with talc was not lower in women who had a tubal ligation [3,4] (and presumably had blocked access to talc).

If we accept that the actual hazard ratio for ever-use versus never-use is 1.2 how are we to interpret this number? If we consider a particular woman who uses talc regularly, her lifetime risk of ovarian cancer would increase from about 1.3% to 1.6%, an increase of 0.3% or three cases in a thousand. On a yearly scale, the risk rises from 20 per 100,000 women per year to 24 per 100,000 per year or four cancer cases for every 100,000 talc users. The latter might strike as more favorable, but, in fact describes the same risk. If we consider the population as a whole, the total number of ovarian cancer cases caused by talc depends on the frequency of talc use in the population. It is right to be concerned over the carcinogenicity of talc even if the risk ratio is low, because up to 50% of women are exposed [1]. If 40% of women use talc and the relative risk is 1.2, then 7% of ovarian cancer cases would be attributable to talc use or 1577 cases a year in the USA. This is not a trivial number and should not be dismissed. If 20% of women were talc users the number of cases per year would be 819. If only 5% of women use talc then the number of cases per year would be 211. Few perhaps, but if ovarian cancer is avoidable, it is best avoided. Is there a downside? Talc affords comfort and was used commonly in the past to control moisture and odor but women have many more choices nowadays. One could of course make a recommendation here not to use talc on sanitary napkins, but this will have little impact because few women continue to use it. In our database of 6000 women from North America that we follow at Women's College Hospital, the use of talc on sanitary napkins has declined precipitously from one generation to the next; talc use was recorded by 11% for women born from 1920 to 1940, but for only 1% of women born after 1975. Similarly, the use of talc applied directly to the genital area fell from 19% to 3% over the same period.

In the interests of public health, I believe we should caution women against using genital talcum powder. However, this policy of talc avoidance is unlikely to have much impact nowadays given this downward trend in usage. I don't think we should try to ascribe any particular case of ovarian cancer to prior talc use. The estimate of a risk ratio of 1.2 provides information about the potential contribution of talc to the burden of ovarian cancer in the population, but is not helpful in determining if a specific case is, or is not, the result of talc exposure. Are we able to make helpful recommendations for women who have used it in the past but who no longer use it? Probably not, we do not offer preventive surgery for women with a risk of ovarian cancer that is less than 2% and screening with CA125 or ultrasound is not recommended to women at average or slightly increased risk.

Conflict of interest

The author declares no conflict of interest.

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